

# Endothelial Function, Lipoproteins, and Cardiovascular Inflammatory Markers in Treated HIV-infected Patients

## with Hyperlipidemia who were Switched to an Atazanavir-Containing Regimen or Continued on Other Protease Inhibitor-Based Therapy: Switch to Atazanavir Brachial Artery Reactivity (SABAR) Study

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### ABSTRACT

**Background:** Protease inhibitor (PI) use has been associated with adverse changes in lipoproteins, endothelial dysfunction and increased cardiovascular disease risk. This study evaluated changes in endothelial function, lipoproteins and cardiovascular inflammatory markers in hyperlipidemic, atazanavir(ATV)-naïve PI-experienced patients who switched their PI to ATV, a PI with a favorable lipid profile.

**Methods:** Prospective, randomized, multinational trial in HIV-infected patients on stable non-ATV PI-containing antiretroviral therapy (ART) with plasma HIV RNA (VL) <500 copies/mL and fasting low-density lipoprotein (LDL) cholesterol >130 mg/dL or triglycerides (TG) >200 mg/dL. Subjects were randomized (1:1) to continue their current PI regimen or switch their PI to ritonavir-boosted ATV for 24 weeks(wks). Brachial artery flow-mediated dilation (FMD) was determined by B-mode ultrasound before switching, at 12 and 24 wks. Lipoproteins were measured by nuclear magnetic resonance spectroscopy and cardiovascular inflammatory proteins were measured by SearchLight assays. Median changes within each arm (signed rank test) and between arms (Wilcoxon test) were calculated.

**Results:** 50 subjects (median age 43 yrs, 84% men, 66% white, 42% current smokers, 30% on stable PI-containing therapy, 5 years prior ART with 30% on ritonavir-boosted PI [80% on lopinavir/ritonavir] were enrolled; all completed the study. At baseline: median VL was <500 c/mL, CD4 count (cells/mm<sup>3</sup>) was 510 for ATV and 486 for PI. FMD was 5.0% and 5.3% in the ATV and PI arms respectively, total cholesterol (TC), LDL, HDL, and TG (mg/dL) were 204, 122, 37, 244 for ATV and 204, 122, 41, 203 for PI arms. At wk 12 and 24, FMD did not change in either group. At wk 24, TC decreased by 25 (p<0.001) in ATV and 1.5 in the PI arm (ns) (between arm p=0.009). TG decreased by 58 (p<0.007) and +3.5 (ns) respectively (between arm p=0.13). There were no significant between arm differences in total or small LDL size, total HDL, or HDL size. Significant and within arm changes were not observed in levels of VL, CD4 count, glucose, adiponectin, leptin, hsCRP, ICAM, VCAM, TNF- $\alpha$ , IP-6, IL-10 or D-dimer.

**Conclusions:** After 24 wks, significant changes in endothelial function and cardiovascular inflammatory markers were not observed in virologically suppressed hyperlipidemic patients on PI-containing ART who switched their PI to ATV in spite of improved TC and TG. CD4 and VL remained stable.

### BACKGROUND

HIV protease inhibitor (PI) use has been associated with adverse changes in lipoproteins, endothelial dysfunction and increased cardiovascular disease risk.

Atazanavir (ATV) is a PI that has less adverse lipid effects than most other PIs.

This study evaluated changes in endothelial function, lipoproteins and cardiovascular inflammatory markers in hyperlipidemic, atazanavir (ATV)-naïve PI-experienced patients who switched their PI to ATV, a PI with a favorable lipid profile.

### PRIMARY OBJECTIVE

To compare the change in brachial artery flow-mediated vasodilation (FMD) from baseline to week 24 in subjects switching to ATV with the change in brachial artery FMD in subjects continuing on a stable PI-based regimen

### METHODS

Prospective, randomized, multinational trial in HIV-infected patients

Inclusion criteria:

- On stable PI-containing ART plus  $\geq 2$  nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) for  $\geq 12$  weeks
- Plasma HIV RNA <500 copies/mL
- Fasting low-density lipoprotein cholesterol (LDL-C) >130 mg/dL OR triglycerides (TG) >200 mg/dL.

Exclusion criteria:

- Prior or current ATV use
- Current use of non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Cardiovascular disease, diabetes mellitus, tobacco use >1 ppd
- Initiation of lipid-lowering drugs within 4 weeks
- Use of systemic immunomodulators, insulin-sensitizing agents, heavy vitamin supplement use

**N = 50 subjects from 6 sites in the U.S., Argentina, and Italy were randomized (1:1) to**

- ATV SWITCH:** switch current PI to ATV (all subjects were on ritonavir (rtv)-boosted PI and switched to ATV 300 mg boosted with rlv 100 mg QD)
- OR**
- PI CONTINUE:** continue current PI-based regimen

All patients continued on current NRTIs

**Study evaluations** (Baseline (prior to switch), Week 12, Week 24):

- FMD, a measure of endothelial function,** was performed by sonographers trained by the University of Wisconsin Atherosclerosis Imaging Research Program, the core laboratory for this study.
- Lower arm occlusion for 5 minutes
- FMD calculated based on arterial diameters 60 seconds after cuff release compared to baseline
- Nitroglycerin-mediated vasodilation (NTGMD) measured 3 minutes after 400 mcg NTG

**Lipoproteins** measured by nuclear magnetic resonance spectroscopy  
**Cardiovascular inflammatory proteins** measured by SearchLight assays

**Insulin and glucose metabolism** measured with oral glucose tolerance test  
 Median changes within each arm (signed rank test) and between arms (Wilcoxon test) were calculated

**Power calculation:** 25 subjects per group will have

- 80% power to detect a difference between groups in mean FMD change of 2.9%, and 90% power to detect a mean FMD change of 3.4%
- 25 patients per group will provide 80% power to detect a difference between groups in mean change in LDL particle number of 324 nmol/L and a mean change in average particle diameter of 0.61 nm

### RESULTS: Baseline Characteristics

	ATV Switch	PI Continue	p value
<b>N = 50</b>			
Age (years)	43	42.5	0.87
Male (%)	85	83	0.90
White (%)	69	63	0.53
Current smokers (%)	39	46	0.66
On lipid-lowering drugs (%)	31	29	0.55
<b>Active as Baseline</b>			<b>Total (%)</b>
Time on ARVs (years)	10	6	6
Ritonavir boosted PI (n)	26	20	46 (92%)
Lopinavir/ritonavir (n)	22	18	40 (80%)
Current Abacavir (n)	9	5	14 (28%)

	ATV Switch	PI Continue	P value
<b>Systolic Blood Pressure (mm Hg)</b>	119 (110-126)	115.5 (108-122)	0.392
<b>Diastolic Blood Pressure (mm Hg)</b>	75 (67-83)	77 (69-82)	0.748
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	25.6 (21.6-28.2)	27.2 (24.5-30.7)	0.120
<b>HIV RNA (&lt;500 copies/mL)</b>	100	96	
<b>CD4 (cells/mm<sup>3</sup>)</b>	510.5 (357-790)	486 (402-674)	0.944
<b>Total cholesterol (mg/dL)</b>	204 (185-232)	204 (158.5-231)	0.404
<b>LDL-C, Direct (mg/dL)</b>	126 (107-148)	127 (89-151)	0.823
<b>LDL-C (mg/dL)</b>	77 (32-49)	40.5 (34-48.5)	0.984
<b>Triglycerides (mg/dL)</b>	244 (171-377)	203 (152.5-319)	0.562
<b>Non-HDL<sub>c</sub> (mg/dL)</b>	170 (148-191)	161 (125.5-185.5)	0.250
<b>Total HDL cholesterol Ratio</b>	4.77 (4.21-6.87)	4.58 (4.14-5.97)	0.516
<b>Lipoprotein(a), (mg/dL)</b>	16.5 (11-37)	27 (7.5-34)	0.288
<b>Non-HDL<sub>c</sub> particles (nmol/L)</b>	98.5 (78.8-133.6)	89.2 (70.9-121.3)	0.892
<b>Large VLDL particles (nmol/L)</b>	8 (0.5-13.6)	4.9 (2.3-12.2)	0.351
<b>VLDL size (nm)</b>	52.6 (50.1-64.4)	54.3 (48.8-63.1)	0.614
<b>LDL particles (nmol/L)</b>	52.9 (23.8-81.5)	72 (34.4-96.7)	0.207
<b>Small LDL particles (nmol/L)</b>	1064.3 (789-1386)	1087.6 (815.2-1336)	0.786
<b>LDL size (nm)</b>	20.2 (19.8-20.6)	20.2 (19.8-20.5)	0.727
<b>HDL particles (nmol/L)</b>	27.5 (25.2-30.4)	27.3 (24.7-30)	0.627
<b>Large HDL particles (nmol/L)</b>	3.4 (1.1-5.5)	3.7 (1.9-4.9)	0.823
<b>HDL size (nm)</b>	8.6 (7.1-11.3)	8.7 (7.5-11.5)	0.298
<b>hs-C-reactive Protein (mg/L)</b>	1.6 (1.1-3.3)	1.5 (1.1-3.5)	0.939
<b>D-dimer (ng/mL)</b>	55.4/47.9 (33/42.9-33/45.900)	82.7/46.0 (40.7/22.0-167.6/49.7)	0.524
<b>IP-6 (ng/mL)</b>	135.3 (92.8-178.8)	119.7 (85.4-164.9)	0.497

> Baseline values of all other markers (bilirubin, glucose, insulin, HOMA-IR, insulin AUC, glucose AUC, adiponectin, leptin, ICAM-1, VCAM-1, IL-10, TNF $\alpha$ ) were similar between arms

### RESULTS: Endothelial Function

	ATV Switch	PI Continue	Between arms
<b>Baseline</b>			
Brachial artery diameter (cm)	4.07 (3.93-4.21)	4.05 (4.007-4.046)	0.778
Flow Mediated Dilation (FMD), %	4.98 (3-7.25)	5.3 (3-6.67)	0.756
Nitroglycerin Mediated Dilation (%)	15.6 (9-19.2)	13.7 (9.91-19.37)	0.444
<b>Week 24</b>			
Brachial artery diameter (cm)	0.437 (0.405-0.51)	0.442 (0.408-0.465)	0.481
Brachial artery diameter (Δ from entry)	0.009 (-0.003-0.02)	0.039 (0.002-(-0.01-0.008)	0.036
FMD (%)	4.05 (2.56-5.89)	4.43 (2.82-6.1)	0.134
FMD (Absolute Δ from entry)	0.16 (1.05-0.98)	0.423 (0.027-0.822)	0.514
NTGMD (%)	14.2 (10.24-16.36)	12.6 (9.43-17.18)	0.956
<b>Week 24</b>			
Brachial artery diameter (cm)	0.407 (0.402-0.525)	0.405 (0.415-0.484)	0.694
Brachial artery diameter (Δ from entry)	0.31 (0.21-0.33)	0.27 (0.26-0.43)	0.534
FMD (%)	1.34 (-2.24-1.83)	0.566 (2.5 (-1.58-1.94)	0.363
FMD (Absolute Δ from entry)	0.28 (0.05-0.52)	0.3 (0.21-0.26)	0.244

> Even after adjustment for changes in brachial artery diameter, the between arms differences in FMD were not significantly different (p=0.64)

### RESULTS: Laboratory Tests

	Week 24	Change Entry to Week 24			p	Week 24	Change Entry to Week 24			p	Between arms
		Median Change	Q1-Q3	Q3			Median Change	Q1 Change	Q3		
<b>N</b>	28					23					
<b>Systolic Blood Pressure (mm Hg)</b>	119	1	(-3-7)	0.647	112	-4	(-9.5-2.5)	0.049	120	0.820	
<b>Diastolic Blood Pressure (mm Hg)</b>	75.5	1	(6.6-10)	0.879	75	-2	(-6-3.8)	0.500	74.8	0.438	
<b>Heart Rate (bpm)</b>	65.5	1	(-3-5)	0.468	63	-2	(-6-10)	0.918	62.0	0.120	
<b>HIV RNA (&lt;500 copies/mL)</b>	92				95.2						
<b>CD4 (cells/mm<sup>3</sup>)</b>	503	1.5	(-52-47)	0.720	543	17	(-40-110)	0.920	539	0.009	
<b>Total cholesterol (mg/dL)</b>	180	-25	(-46-14)	0.000	205.5	1.5	(-25-31)	0.975	209	0.009	
<b>LDL-C, Direct (mg/dL)</b>	122	4	(-25-6)	0.097	128	2	(-7-20)	0.575	125	0.125	
<b>HDL-C (mg/dL)</b>	36	-2	(-8-2)	0.306	40	-3	(-9-6)	0.987	40.1	0.831	
<b>Triglycerides (mg/dL)</b>	195	-58	(-157-9)	0.001	206.5	3.5	(-43-68)	0.615	0.813		
<b>Non-HDL cholesterol (mg/dL)</b>	143	-27	(-41-11)	0.000	156	0.5	(-26-40)	0.975	0.814		
<b>HDL cholesterol Ratio</b>	4.6	-0.1	(-0.2-0.8)	0.093	5	0.1	(-0.9-1.1)	0.872	0.969		
<b>Lipoprotein(a), (mg/dL)</b>	16	-1	(-6-0)	0.309	26	0	(-12-4)	0.447	0.896		
<b>VLDL particles (nmol/L)</b>	86.9	-18.9	(-28.1-4.8)	0.005	97.9	-8.1	(-29.0-12.6)	0.096	0.096		
<b>Large VLDL particles (nmol/L)</b>	7.2	-3.2	(-8.8-1.1)	0.000	7.6	1.6	(-6.1-6.9)	0.516	1.25		
<b>VLDL size (nm)</b>	52.9	-3	(-11.8-3.3)	0.156	56.1	-1.7	(-11.7-10)	0.953	42.9		
<b>LDL particles (nmol/L)</b>	52.9	-2.4	(-10.2-19.5)	0.278	63	-6.6	(-29.0-22.3)	0.814	0.849		
<b>LDL particles (nmol/L)</b>	1121.4	-193.9	(-389.9-25.7)	0.000	1001.7	-115.8	(-335.1-83.8)	0.407	0.141		
<b>Small LDL particles (nmol/L)</b>	877.1	-116.8	(-392.9-16.7)	0.010	1124.5	-163.1	(-394.2-263.1)	0.478	0.741		
<b>LDL size (nm)</b>	20	0	(-0.33-0.6)	0.612	20.2	0.3	(-0.4-0.7)	0.220	0.541		
<b>HDL particles (nmol/L)</b>	26.3	-0.7	(-4-1.7)	0.120	27.3	0.3	(-2.5-3.1)	0.486	0.164		
<b>Large HDL particles (nmol/L)</b>	3.2	-0.1	(-1-1.2)	0.912	4.2	-0.2	(-0.6-1.7)	0.837	0.992		
<b>HDL size (nm)</b>	8.6	0	(-0.3-0.2)	0.815	8.6	0	(-0.1-0.2)	0.702	1.000		
<b>hs-Creactive Protein (mg/L)</b>	2.2	0.3	(-1.1-3)	0.343	3.5	0.5	(-0.9-4.2)	0.328	0.739		
<b>D-dimer (ng/mL)</b>	82.8/49.0	1.626/-0.7	(-2.866/-0.136E+08)	0.177	77.8/74.0	0.162E+08	(-7.626E+07-3.0E+07)	0.555	0.100		
<b>IP-6 (ng/mL)</b>	139.7	-3.3	(-9.1-24)	0.702	116.9	6.3	(-2.3-45.2)	0.860	0.992		
<b>Total bilirubin (mg/dL)</b>	2.3	1.45	(0.8-2.8)	0.000	0.6	0	(-0.2-0.1)	0.430	0.020		
<b>Albumin (g/dL)</b>	4.0	0.0	(-1.1-5.1)	0.21	100	0	(-1.8-9)	0.625	0.425		
<b>Serum Insulin (uIU/mL)</b>	11	0	(-0.7-3.5)	0.762	7.9	1.1	(-2.7-0.6)	0.319	0.307		
<b>Glucose AUC</b>	437	-23.5	(-43-12)	0.565	470	22	(-52-56)	0.825	0.170		
<b>Insulin AUC</b>	7.7	0.5	(-0.4-2)	0.320	120	25	(-24-22)	0.270	0.270		
<b>HOMA-IR</b>	2.64	0	(-1.0-1.8)	0.676	1.85	0.3	(-0.1-2)	0.478	0.357		

> Median changes in values of all other markers (adiponectin, leptin, ICAM-1, VCAM-1, IL-10, TNF $\alpha$ ) were similar both within (all p>0.5) and between arms (all p>0.5)

### CONCLUSIONS

- Plasma HIV RNA and CD4 count remained stable.
- Compared to subjects who continued their PI regimen, those who switched to ATV had :
  - Significant reductions in total cholesterol, triglycerides, and non-HDL cholesterol
  - Significantly higher bilirubin
  - No significant changes in endothelial function and cardiovascular inflammatory markers
- Among virologically suppressed dyslipidemic individuals on PI therapy, switching to atazanavir did not change endothelial function or cardiac biomarkers, despite improvements in lipids.

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